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Predicting outcomes in pulmonary arterial hypertension based on the 6-minute walk distance

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KEYWORDS:
6-minute walk distance;
pulmonary arterial hypertension;
survival outcomes;
prognostic value;
surrogate end points

BACKGROUND: Clinical studies of pulmonary arterial hypertension have used the change in the 6-minute walk distance (6MWD) as a clinical end point; however, its association with survival outcomes has not been well established. In this analysis, we examined the prognostic value of the baseline 6MWD, absolute thresholds of the 6MWD, and change in the 6MWD.

METHODS: Patients in the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) with 6MWD at enrollment, with or without a follow-up assessment within the first year of observation, were included. Kaplan-Meier survival estimates were computed for sub-sets with baseline 6MWD results that were above or below all possible thresholds and for sub-sets with a change in the 6MWD that was 10 percentage points above or below all possible thresholds, including improvement thresholds and worsening thresholds. Multivariable Cox regression models assessed the effect of improvement and worsening in the 6MWD on 1-year survival, adjusted for baseline factors.

RESULTS: One-year survival estimates were higher for patients with a baseline 6MWD above vs below a threshold, although no specific threshold was more prognostic than another. In a model adjusted for the baseline 6MWD and risk score, worsening of the 6MWD over time significantly predicted decreased survival, but improvement in the 6MWD did not affect survival.

CONCLUSIONS: No 6MWD improvement threshold carries particular prognostic value. Improvement in the 6MWD was not associated with survival, but worsening of the 6MWD was strongly and significantly associated with poor prognosis.

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The 6-minute walk test measures exercise tolerance.[1] The distance covered during a 6-minute walk (6MWD) is an indicator of the ability to perform activities of daily life. This, along with observations that exercise tolerance predicts treatment effect in clinical studies of cardiovascular disease,[2] has led to the acceptance of the 6MWD as an unvalidated surrogate of survival outcomes in studies of pulmonary arterial hypertension (PAH). Similarly, a 15% decrease in the 6MWD coupled with other clinical markers or biomarkers suggesting deterioration has been included in definitions of "time to clinical worsening" end points.[3] Improvement in the 6MWD has also been equated with improved quality of life.[4] Although the use of the 6MWD as

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a surrogate end point has allowed shorter, smaller clinical studies in PAH,[5] the use of the 6MWD as a surrogate of survival outcomes has not been fully validated.

Most studies of the 6MWD in PAH have found a relationship between the baseline 6MWD and mortality and survival[6–10]; other studies have not.[11] Some studies have found a specific 6MWD threshold (e.g., 380 or 440 m) to predict survival, but these were not randomized, controlled studies, and the numeric value of the walk was actually the mean walk achieved in the open-label patients that were studied.[6,12] Evaluation of the percentage-predicted 6MWD[13] found it was no more predictive than the absolute 6MWD.[14] Change in the 6MWD has not been shown to predict survival,[15] largely because individual clinical studies have not been designed to evaluate mortality and survival. Improvement in the 6MWD of $\geq$41.8 m was recently found to correlate with lowered odds of a clinical event at 12 weeks, but this accounted for only 22% of the treatment effect, suggesting that change in the 6MWD alone is at best a modestly valid surrogate end point for clinical events.[16] Thus, current data suggest that the 6MWD has prognostic value at baseline but that the value of this parameter alone as a marker of clinical status beyond baseline may be limited.

Currently available studies that have examined change in the 6MWD have focused primarily on mean change and not on absolute increases or decreases in the 6MWD; that is, the relative value of improving or worsening. Nevertheless, clinicians continue—without substantiation—to rely on this parameter as a surrogate for survival in patients with PAH.[15] Furthermore, studies have historically emphasized improvement in the 6MWD as the primary end point, whereas deterioration of the 6MWD has had only limited use as a component of a composite worsening end point.[3]

The Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) is the largest multicenter, observational United States–based registry of patients with PAH established to date.[17] A primary objective of REVEAL is to characterize the clinical features and outcomes of patients with PAH currently under care at PAH centers. In this report, data from REVEAL were used to evaluate the prognostic value of baseline 6MWD values and change in the 6MWD over time to gain insight into the clinical significance of absolute increase vs decrease in the 6MWD. Specifically, we examined the prognostic value of the baseline 6MWD, absolute thresholds of the 6MWD, and change in the 6MWD.

Methods

Study design and patients

The design of REVEAL, including inclusion and exclusion criteria, has been described previously.[17] Briefly, REVEAL is an observational, prospective registry involving 55 university-affiliated and community hospital–based PAH centers in the United States. Patients who met the modified World Health Organization (WHO) definition for Group 1 pulmonary hypertension[18] and expanded hemodynamic criteria (mean pulmonary arterial pressure [PAP] $>$ 25 mm Hg at rest or $>$ 30 mm Hg with exercise; mean pulmonary capillary wedge pressure [PCWP] or left ventricular end-diastolic pressure of $\leq$18 mm Hg, measured contemporaneously with PAP; pulmonary vascular resistance of $\geq$240 dyn $\cdot$ s $\cdot$ cm^{-5}) were enrolled consecutively from March 2006 through December 2009.

The Institutional Review Board of each participating center reviewed the protocol, and all participants or their legal guardians provided written informed consent before study entry. The data download for this analysis occurred on February 4, 2013, and included patients meeting expanded as well as traditional, hemodynamic criteria.

Data collection

Demographics, medical history, PAH-specific and concomitant medications, diagnostic procedures, pulmonary function tests, the 6MWD, and hemodynamics were collected at the baseline assessment. Data collected retrospectively included time of diagnosis and symptom onset, specialty of evaluating physicians, tests used to diagnose PAH, WHO Group I classification, and use of PAH-specific medications. After meeting enrollment criteria, no tests or study visits were required, but data were collected prospectively every 90 days, including PAH treatments, concomitant treatments, diagnostic procedures, and outcomes.

Analytic cohort

For this analysis, REVEAL patients were included if they had WHO Group I PAH, were aged $\geq$18 years at enrollment, had PCWP of $\leq$15 mm Hg, and met the right heart catheterization criteria at rest. Further selection criteria included an available 6MWD measure at enrollment (also referred to as "baseline 6MWD"), and for analyses examining change in the 6MWD, a follow-up 6MWD measure within 12 months of enrollment. As a sensitivity analysis, the population was further restricted to newly diagnosed patients for the evaluation of the prognostic importance of change in the 6MWD.

Statistical analysis

Baseline demographic and clinical characteristics are summarized using percentages for categoric variables and means $\pm$ standard deviation for continuous variables and summarized for patients with the baseline 6MWD only and patients with baseline and follow-up 6MWD results. Pearson's correlation was used to evaluate associations between the 6MWD and other variables at enrollment.

Kaplan-Meier estimates were computed for patient sub-sets with 6MWD results that were above, below, or at specified 6MWD thresholds ($<$165 m; 165–440 m; $>$440 m), which have shown prognostic value in the 19-variable REVEAL Risk Score, an algorithm that predicts 1-year survival in PAH patients.[19] All possible above and below thresholds were considered, such that the 1-year Kaplan-Meier estimate at a given threshold could be plotted against the threshold. The above and below estimates are similar to the points that would be plotted on a receiver operating characteristic (ROC) curve, except that a time-to-event outcome is used instead of a simple binary outcome. Unlike an ROC analysis, this approach could be extended for specific bandwidths of interest (e.g., $\pm$10 percentage points for change in the 6MWD), where all possible midpoints are considered. The resulting plots are similar to moving averages, except that the value on the *y*-axis is a Kaplan-Meier estimate instead of a simple average (this is also similar to a kernel smoother where a uniform distribution is used as the kernel instead of a more complex function). In this way, each point on the

plot can be interpreted more simply as a Kaplan-Meier estimate for a particular cohort.

The graphic analyses were not adjusted for group differences. Therefore, Cox regression analysis was used to generate hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk associated with improvement or worsening in the 6MWD (per 15%) from the time of the follow-up 6MWD assessment within 1 year of enrollment. Models were adjusted for the baseline 6MWD and for the baseline 6MWD and REVEAL Risk Score.[19] To reduce the effect of outliers, improvement and worsening were both capped at 45%.

Results

Of 3,515 patients enrolled in REVEAL, 2,370 had baseline 6MWD results and 1,798 of these also had at least 1 follow-up 6MWD assessment during the first year after enrollment (Figure 1). Patient demographics and disease characteristics at enrollment were similar between patients with a baseline 6MWD only and patients with a baseline and follow-up 6MWD (Table 1). The mean age for each group was approximately 52 years, and most patients were women. About 20% in each group was newly diagnosed with PAH, the primary etiology was idiopathic PAH, followed by connective tissue disease, and 55.7% of patients wtih 6MWD at enrollment and 53.9% of patients with follow-up 6MWD ≤1 year were categorized as New York Heart Association (NYHA) Functional Class III or IV.

The mean 6MWD at enrollment into REVEAL was 360 ± 129 m. Compared with the most recent hemodynamic assessment, the 6MWD was negatively correlated with mean right atrial pressure ($\rho = -0.198$, $p < 0.001$), and PCWP ($\rho = -0.077$, $p < 0.001$) and positively correlated with cardiac output ($\rho = 0.131$, $p < 0.001$). No significant correlation existed with pulmonary vascular resistance or MPAP. The 6MWD significantly correlated with oxygen saturation at rest ($\rho = 0.151$, $p < 0.001$) and to a lesser extent at end of the walk ($\rho = .049$, $p < .001$).

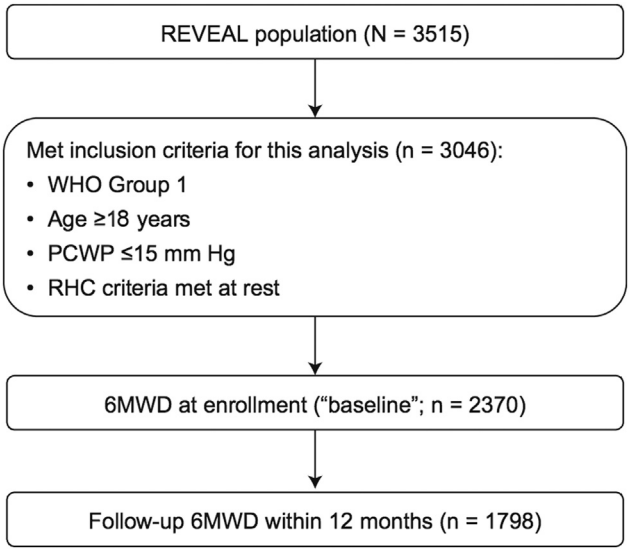

Figure 1 Diagram of patients included in the analysis cohort. 6MWD, 6-minute walk distance; PCWP, pulmonary capillary wedge pressure; RHC, right heart catheterization; WHO, World Health Organization.

Table 1 Patient Demographics and Disease Characteristics At Enrollment

Parameter[a]	Patients with 6MWD at enrollment (n = 2,370)	Patients with follow-up 6MWD ≤ 1 year (n = 1,798)
Age, years	52.2 ± 14.6	51.7 ± 14.5
Female	1,872 (79.0)	1,438 (80.0)
Newly diagnosed	525 (22.2)	417 (23.2)
PAH etiology		
Idiopathic	1,088 (45.9)	848 (47.2)
Familial	67 (2.8)	53 (3.0)
Associated		
Congenital heart disease	247 (10.4)	181 (10.1)
Connective tissue disease	632 (26.7)	476 (26.5)
Portopulmonary hypertension	129 (5.4)	84 (4.7)
HIV	38 (1.6)	26 (1.5)
Drugs and toxins	143 (6.0)	111 (6.2)
Other	26 (1.1)	19 (1.1)
NYHA Functional Class		
III or IV	1,235 (55.7)	921 (53.9)
6MWD at enrollment, m	360 ± 129	370 ± 122

6MWD, 6-minute walk distance; HIV, human immunodeficiency virus; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension.

[a]Continuous data are shown as mean ± standard deviation and categoric data as number (%).

Survival by 6MWD thresholds

When stratified by the baseline 6MWD, survival estimates were lower for patients with a baseline 6MWD below the 165-m threshold than for patients in the 2 groups with a baseline 6MWD above 165 m (Figure 2). Conversely, patients with a baseline 6MWD above the 440-m threshold had better survival than patients in the 2 groups with a baseline 6MWD below 440 m.

To determine whether this observation held true for any 6MWD threshold, we calculated the 1-year Kaplan-Meier survival estimates for patients with a baseline 6MWD below and above all possible 6MWD threshold values. In this graphic analysis, each cohort of interest was represented by a single point on the dashed line or the solid line shown in Figure 3, instead of a full curve over time, as in Figure 2. For example, the survival estimate of patients with a baseline 6MWD above 440 m was 96.9% at 1 year (Figure 2, white star) and was represented by a single point on the black dashed line in Figure 3 (white star). In Figures 2 and 3, the cohort of 204 patients with a baseline 6MWD below 165 m is marked with a black star. Moving from left to right along the black curve in Figure 3, an

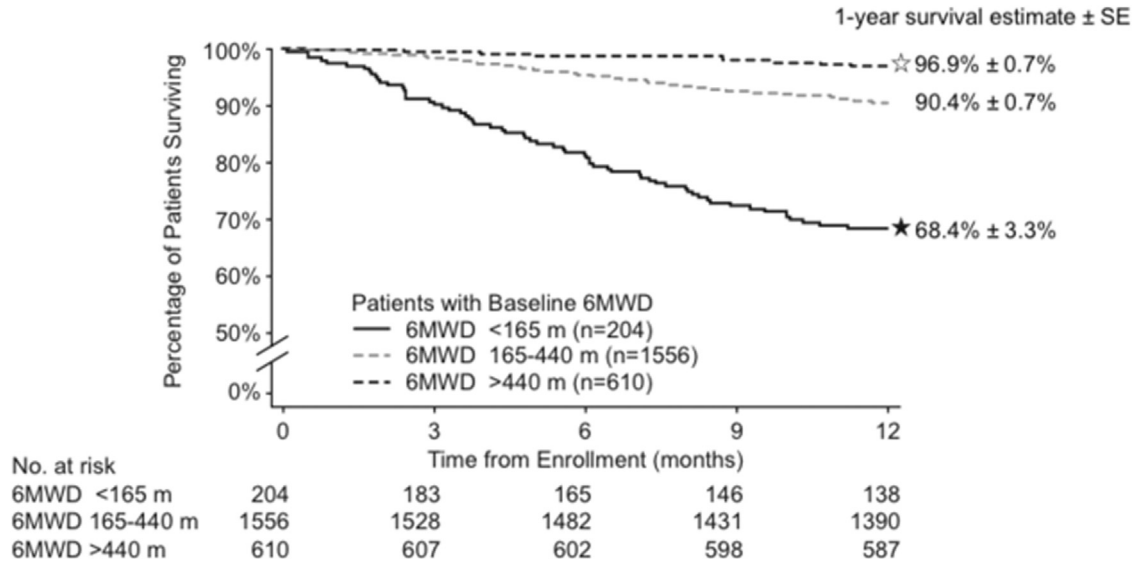

Figure 2 Kaplan-Meier survival estimates based on absolute 6-minute walk distance (6MWD) thresholds at 165 m and 440 m, and all possible 6MWD thresholds. One-year survival estimates are shown for patients with a baseline 6MWD <165 m (black solid), 165–440 m (gray dashed), and >440 m (black dashed). Stars mark the 1-year survival estimates for patients with a 6MWD of >440-m threshold (white star) and patients with a 6MWD of ≤165-m threshold (black star), and show the relationship between the two figures. SE, standard error.

increasing number of patients in the middle cohort (baseline 6MWD = 165–440 m) is included in the estimate. At the far right of the black curve (Figure 3), virtually every patient is included, and the curve meets an asymptote of the survival estimate for the full population of patients with a non-missing 6MWD (90.3%). Analogously, a white star in Figures 2 and 3 marks the 1-year survival estimate for the cohort of 610 patients with a baseline 6MWD exceeding 440 m. Moving from right to left along the dashed curve in Figure 3, an increasing number of patients in the middle cohort (baseline 6MWD = 165–440 m) is included in the estimate, thereby reducing the estimated 1-year survival. At the far left of the dashed curve, virtually every patient is included, and the low point of the dashed curve therefore matches the high end of the solid curve. Both curves become "smoother" as they approach the full population estimate because the sample size gets larger.

Regardless of the baseline 6MWD threshold used, 1-year survival estimates were lower for patients with a baseline 6MWD below the threshold than for patients with a baseline 6MWD above the threshold (Figure 3; solid black vs dashed black line), indicating a survival advantage associated with having a baseline 6MWD above any threshold.

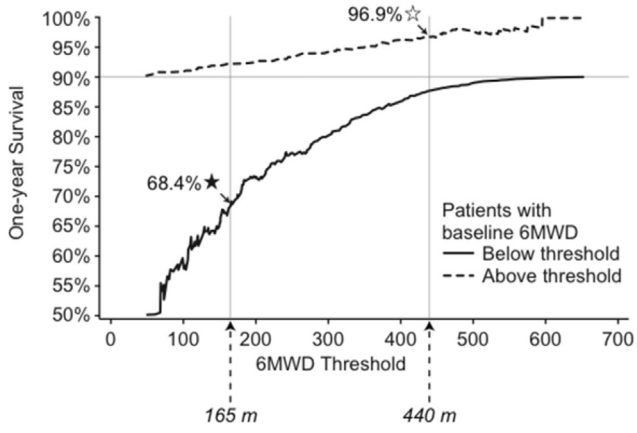

Figure 3 One-year survival estimates for patients with the most recent 6-minute walk distance (6MWD) at enrollment above (black dashed) and at or below (black solid) all possible 6MWD thresholds. One-year survival estimate for the entire analysis cohort was 90.3% (horizontal gray line). Stars mark the 1-year survival estimates for patients with s 6MWD >440-m threshold (white star) and patients with a 6MWD of ≤165 m threshold (black star), and show the relationship between the 2 figures. SE, standard error.

Survival by change in the 6MWD

Significant between-patient differences may not necessarily translate to significant prognostic value for within-patient differences. To determine whether change in the 6MWD over time has clinical value, an analysis was done to estimate survival for all patients (Figure 4) and newly diagnosed patients (Figure 5) who experienced any

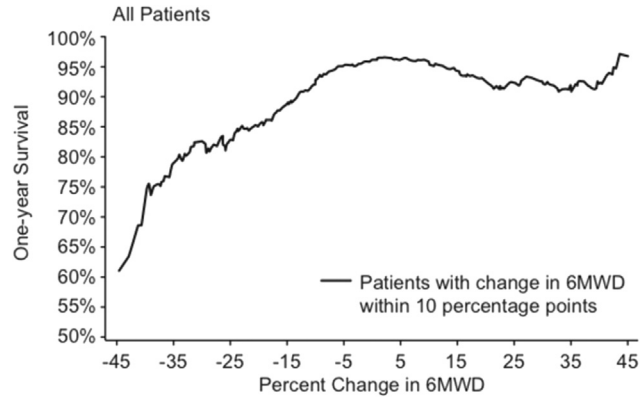

Figure 4 Kaplan-Meier survival estimates based on the percentage change in the 6-minute walk distance (6MWD) ±10 percentage points for all patients with a baseline 6MWD and follow-up 6MWD within 1 year.

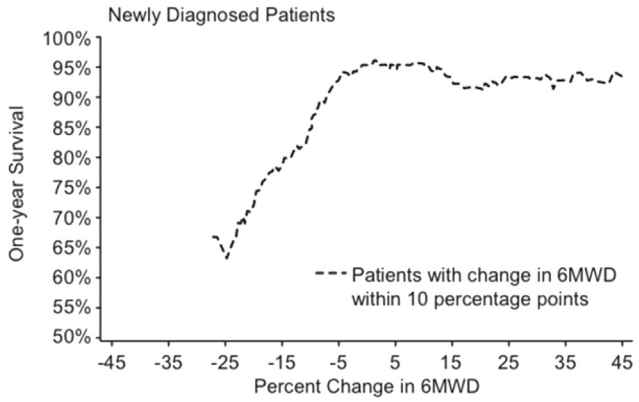

Figure 5 Kaplan-Meier survival estimates based on the percentage change in the 6-minute walk distance (6MWD) ±10 percentage points for newly diagnosed patients with a baseline 6MWD and follow-up 6MWD within 1 year.

percentage change in the 6MWD ±10 percentage points. For all patients, 1-year survival estimates peak for patients with the smallest percentage change in the 6MWD over time (e.g., 1-year survival estimate is 95.9% for patients with 0 ± 10 percentage points change in the 6MWD; Figure 4). This result was not unexpected because the patients with no change or <15 percentage points of change in either direction had higher a mean 6MWD at enrollment (405 ± 105 m) than patients with ≥15 percentage points of improvement (263 ± 111 m) or ≥15 percentage points of worsening (350 ± 121 m). Repeating the analysis for newly diagnosed patients showed similar results: 1-year survival estimates were highest for patients with the least percent change in the 6MWD over time (Figure 5).

Effect of change in the 6MWD on survival

Multivariable Cox models were used to assess the effect of change in the 6MWD on 1-year survival from the time of the follow-up 6MWD assessment, accounting for the observation that patients who improved more had a lower 6MWD at baseline (Table 2). When the effect of percentage change in the 6MWD was adjusted for a baseline 6MWD or for a baseline 6MWD and REVEAL Risk Score (a measure of overall disease severity), improvement in the 6MWD over time was not associated with better survival (p = not significant per 15% increment of positive change), compared with no change (stable 6MWD), but worsening of the 6MWD was associated with significantly lower survival at 1 year ($p < 0.001$ per 15% increment of negative change). To summarize the results of these analyses:

1. One-year survival is better for patients with a baseline 6MWD above than below a threshold, regardless of what that threshold is (Figure 3).
2. Worsening of the 6MWD over time is associated with lower 1-year survival, but the effects of a stable 6MWD and improvement in the 6MWD over time on 1-year survival are similar. This is true for all patients in the analysis cohort (Figure 4) and for newly diagnosed patients in the analysis cohort (Figure 5).

Table 2 Models of Survival From the Time of Follow-up 6-Minute Walk Distance Assessment Within 1 Year of Enrollment

Model and risk factors	HR (95% CI)	p value
Unadjusted		
Improvement in 6MWD (per 15%[a])	1.21 (1.15–1.29)	<0.001
Worsening in 6MWD (per 15%[a])	1.29 (1.20–1.38)	<0.001
Adjusted for baseline 6MWD		
Improvement in 6MWD (per 15%[a])	1.06 (0.99–1.13)	0.082
Worsening in 6MWD (per 15%[a])	1.21 (1.13–1.30)	<0.001
Adjusted for baseline 6MWD and REVEAL Risk Score		
Improvement in 6MWD (per 15%[a])	1.06 (0.99–1.13)	0.078
Worsening in 6MWD (per 15%[a])	1.20 (1.12–1.29)	<0.001

6MWD, 6-minute walk distance; CI, confidence interval; HR, hazard ratio; REVEAL, Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management.

[a]To reduce the effect of outliers, improvement and worsening were capped at 45%.

3. In models adjusted for the baseline 6MWD or for the baseline 6MWD and REVEAL Risk Score, worsening of the 6MWD over time is significantly associated with poorer survival (Table 2).

Discussion

This study prospectively examined the distinct effects of absolute increase vs decrease in the 6MWD on survival in a large observational cohort of patients with Group I PAH. A major finding in this analysis was that worsening in the 6MWD over time negatively affected survival and was significantly associated with poor prognosis. In addition, the effect of improvement was not meaningfully different from that of stabilization of the 6MWD. Although change in the 6MWD over time affected prognosis, it is important to understand that the effect of improvement in the 6MWD on prognosis was much smaller than the effect of worsening of the 6MWD. Our findings show there is no threshold for percentage change in the 6MWD that is more prognostic than any other but do suggest that a 15% reduction in the 6MWD may be clinically meaningful. This supports the use of a 15% reduction in the 6MWD as a criterion for PAH worsening in clinical studies.[3,20]

The finding that improvement in the 6MWD was not associated with survival, but rather, that deterioration in the 6MWD adversely affects survival, may explain why change in the 6MWD alone had not been found previously to correlate consistently with prognosis. Furthermore, we speculate that this is related to the concept that change in the 6MWD is inversely correlated with the baseline 6MWD. In other words, the patients with the greatest "room for improvement" were those who had the lowest baseline 6MWD values. Thus, when baseline disease severity is taken into account in the adjusted models, the effect of the 6MWD improvement on survival is no longer significant. Percentage change in the 6MWD is subject to greater

variation when the denominator—in this case, the baseline 6MWD value—is low, with a negative percentage change, in particular, being sensitive to baseline differences.

Our analysis of the prognostic value of the 6MWD showed that the baseline 6MWD is an important prognostic factor and that there is no specific 6MWD threshold value that is "special" or more clinically significant than any other. Had we taken an ROC approach to the analysis, we could have identified a specific threshold that was the most predictive of survival by some statistical criteria, but our data suggest that there is little possible clinical advantage to finding a single "best" threshold. In addition, the long-term survival data provided a more natural interpretation of predictive values rather than relying on measures of sensitivity and specificity, which can sometimes be misinterpreted in ROC analyses.[21] The critical points of our findings are: (1) regardless of the 6MWD threshold value used, having a 6MWD above that threshold is better than having a 6MWD below; and (2) the survival gap is much greater for low 6MWD thresholds than it is for higher thresholds.

Several limitations could have affected our analysis: First, this was not a randomized comparison between patients with improvement vs worsening of the 6MWD over time.

Second, the evaluation of baseline data was a univariable analysis. The thresholds of 440 m and 165 m were examined in our analysis because these have shown prognostic value in the 19-item REVEAL risk model.[19] These 6MWD thresholds are relatively extreme but nevertheless have prognostic utility as part of a complex model of risk in which the contributions of many other parameters to the overall risk calculation compensate for any potential bias stemming from these 6MWD thresholds. Therefore, reference to specific 6MWD threshold values may retain some utility in multifactorial assessments, even if the use of "thresholds" is not biologically correct. Miyamoto et al[8] showed prognostic value for a baseline 6MWD cut point of 332 m.

Third, "newly diagnosed" is not the same as "newly treated." Patients enrolled in REVEAL did not undergo any protocol-driven assessments, only clinically indicated assessments, which may or may not have been performed in routine practice as a means to evaluate response to treatment. In this analysis, the time between the baseline and follow-up assessment of the 6MWD varied by patient.

In conclusion, the baseline 6MWD has prognostic value. Worsening of the 6MWD over time is strongly and significantly associated with poor prognosis. The 6MWD should be thought of as a continuum: although having a higher 6MWD is generally better than having a lower 6MWD, there is no "cliff" or specific absolute 6MWD at baseline that is more predictive than any other. Maintaining a stable 6MWD over time is important. An improving 6MWD is also worthwhile—but only insofar as it means the patient is not worsening; an improving 6MWD in itself is unlikely to appreciably affect survival. Patient care may therefore be enhanced by regular 6MWD monitoring, and a decrease of 15% may warrant a more aggressive approach to treatment.

Disclosure statement

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Harrison W. Farber, MD, serves as a consultant and is on the speaker's bureau for Actelion, Ikaria, BMS, Bayer, United Therapeutics, and Gilead, receives grant/research support from Gilead and United Therapeutics, and has received honoraria for his service on the REVEAL Registry Steering Committee, which is supported by Actelion Pharmaceuticals US Inc on behalf of Cotherix Inc. Dave P. Miller, MS, is an employee of ICON Clinical Research, the biostatistics CRO for the REVEAL Registry. Michael D. McGoon, MD, has served as the primary investigator for grants received by his institution from Gilead Sciences Inc and Medtronic Inc, has served on advisory, steering, and/or end point/Data and Safety Monitoring Board committees for Actelion Pharmaceuticals US Inc, Gilead Sciences Inc, Lung LLC, and GlaxoSmithKline, has received honoraria for speaking at conferences supported by Actelion Pharmaceuticals US Inc and Gilead Sciences Inc, and has received honoraria for his service on the REVEAL Registry Steering Committee, which is supported by Actelion Pharmaceuticals US Inc on behalf of Cotherix Inc. Adaani E. Frost, MD, has received honoraria for service on steering committees or advisory boards (or as a consultant) to the following companies working in the area of pulmonary hypertension: Actelion/CoTherix, Gilead, Pfizer, United Therapeutics/Lung Rx, GlaxoSmithKline, Lilly/ICOS, Bayer, Ikaria, and Arena, has received grant support for clinical studies from Ventripoint, GlaxoSmithKline, Actelion, Gilead, Pfizer, United Therapeutics/Lung Rx, Intermune, Stomedix, Bayer, and Novartis, and has received honoraria for her service on the REVEAL Registry Steering Committee, which is supported by Actelion Pharmaceuticals US Inc on behalf of Cotherix Inc. Wade W. Benton, PharmD, is an employee of Actelion Pharmaceuticals US Inc. Raymond L. Benza, MD, has received grant support from United Therapeutics, Gilead, Ikaria, and GeNo, and has received honoraria for his service on the REVEAL Registry Steering Committee, which is supported by Actelion Pharmaceuticals US, Inc. on behalf of Cotherix Inc.

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